Rejection under 35 U.S.C. § 103(a)

Claims 43-44, 46-49, 61-62, and 64-66 remain rejected under 35 U.S.C. § 103(a) as unpatentable over Carter further in view of Chester, et al.

The Examiner asserts that Carter clearly teaches a Fab fusion with other molecules and with another Fab. The Examiner further asserts that it would have been obvious to produce a $F(ab)_2$ with a toxin or enzyme at the CL or Ch1 in view of Chester who teaches fusion proteins to Fabs and scFv fragments where the toxin or enzyme is at the CL.

Claims 43-44, 46-49, and 61-66 remain rejected under 35 U.S.C. § 103(a) as unpatentable over Carter further in view of Tutt et al.

The Examiner states that the rejection of claim 63 is maintained because it would be obvious to produce trispecific Fabs with cross linking according to Tutt et al. in combination with the teaching of Carter on Fab-SH and bispecific molecules.

It is not clear from the wording of this rejection if claims 43-44, 46-49, and 61-66 remain rejected or if this ground of rejection only refers to claim 63.

Applicants' invention

In one embodiment, Applicants' invention relates to an efficient recombinant method to make heterodimers. That is, Applicants recombinantly express a heavy chain (VH-CH1, without a hinge region) fused to a molecule X (3' or 5') and a light chain (VL-CL) fused to a second molecule Y (3' or 5'). These are expressed in a eucaryotic cell to obtain a secretable Fab fragment containing at least two additional molecules X and Y.

To the extent that the present claims contain process limitations, as is well known to the Examiner, the patentability of a product-by-process claim does not reside in the process steps but rather in the characteristics of the product. See M.P.E.P. 2113. Nevertheless, the multipurpose antibody derivatives obtained by the above-described methods are different from the prior art derivatives in that homodimerization through the hinge region is avoided by excluding this region. This feature distinguishes the multipurpose antibody derivatives of the claimed invention from the chemically synthesized or chemically coupled antibody derivatives of the prior art in which coupling is done through the hinge region. $F(ab')_2$ derivatives coupled via the hinge region are also known.

The Carter reference

The prior art describes completely different antibody derivatives. For example, Carter describes the preparation and use of a Fab containing at least one hinge region cysteine present as a free thiol (Fab'-SH) (column 5, lines 18-30). Carter states that "the objects of this invention are accomplished by a method for the production of a Fab' antibody polypeptide having at least one hinge region cysteine present..." (col. 5, lines 18-20) and further states that it "would be desirable to produce stable Fab'-SH polypeptides which may be conveniently coupled in vitro to form bivalent Fv or $F(ab')_2$ molecules." (col. 4, lines 21-24). Thus, in the teaching of Carter, the cysteinyl residue is used to couple a molecule chemically to the Fab fragment, resulting in $F(ab')_2$ molecules. As taught by Carter, two Fab' fragments (which both contain hinge regions by definition, see col. 1, lines 64-67) are produced recombinantly (see, for example, col. 5, line 54 to col. 6, line 7). These recombinantly produced Fab' fragments are then covalently bound together by in vitro methods which are known in the art (see col. 6, lines 10-16). Preferred chemical methods of forming the covalent bonds between the free thiol cysteinyl residues are set forth in col. 6, lines 16-25.

Thus, Carter does not teach or suggest heterodimers wherein the CH1 domain is not linked to a hinge region. Additionally, Carter does not teach or suggest heterodimers containing at least two other molecules X and Y.

The secondary references

The secondary references fail to correct the deficiencies of Carter. The Examiner asserts that Chester et al. clearly teach fusion proteins to Fabs and scFv fragments with a toxin or enzyme at the CL and that it would be obvious to produce a $F(ab)_2$ with a toxin or enzyme at the CL or CH1.

In response, Applicants note that Chester et al. present a very generalized review. Figure 1 of this review shows a Fab with a fused toxin or enzyme on the CL of the light chain. However, there is nothing in this review that would provide motivation to one of ordinary skill in the art to fuse two molecules to the Fab. Furthermore, the $F(ab')_2$ derivatives shown are homodimers coupled via the hinge region.

As is well-known to the Examiner, prima facie obviousness requires that three criteria be met. First, the prior art reference or references must teach or suggest all claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in

the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings in a manner which renders the claimed invention obvious. Third, there must be some reasonable expectation of success of achieving the claimed invention when the references are combined in the manner being relied on for establishing obviousness. See MPEP section 2142.

In the present case, Carter and Chester et al. together do not teach or suggest all of the claim limitations. Neither Carter nor Chester et al. teach or suggest a heterodimer coupled without using the hinge region. Neither Carter nor Chester et al teach heterodimers containing at least two other molecules X and Y. Furthermore, there is no suggestion or motivation in Chester et al. to modify the teaching of Carter to achieve Applicants' claimed invention.

Turning to the Tutt et al. reference, The Examiner asserts that Tutt et al. teach trispecific antibodies and that in combination with Carter's teaching on Fab-SH molecules, it would be obvious to produce trispecific Fabs with crosslinking.

However, Figure 1 of Tutt, et al. shows trispecific Fabs which contain hinge regions and which are chemically coupled onto phenylenediamaleimide. There is nothing in Tutt et al. to teach or suggest the use of Fabs to form heterodimers and there is nothing to teach or suggest coupling antibodies without inclusion of the hinge region.

In summary, the multipurpose antibody derivatives of Applicants' claimed invention differ from the prior art antibody derivatives in that they are heterodimers, comprising a VL-CL-VH-CH1 scaffold, not coupled to other molecules by the thiol groups in the hinge region, but linked by peptide linkers as short as a few amino acids (see present specification, page 5, lines 10-11) and further containing at least two additional molecules.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: Jan. 24, 2003

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